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Casimir Jones, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
GOLDBERG, JEANINE ANNE	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/613,887
Filing Date: July 11, 2000
Appellant(s): HOGAN, KIRK

David Casimir
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed August 27, 2009 appealing from the Office action mailed May 21, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The current appeal in this application is substantially identical to the appeal filed on September 19, 2005 in the instant application. The Board of Appeals affirmed the examiner in a Decision mailed July 25, 2006.

A copending application 09/976,423 is similarly under appeal. The '423 application has a pending Appeal Brief.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The statement of the status of the amendments in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

- Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981)

- Quane et al (Human Molecular Genetics, Vol. 3, No. 3, page 471-476, 1994)
- Acta Anaesthesiologica Scandinavica (Vol. 39, page 139-141, 1995)
- La Du (Cellular and Molecular Neurobiology, Vol. 11, No. 1, page 79-89, 1991)
- Pharmacogenetics (Chapter 4, pages 309-326, IDS #201)
- Evans et al (Science, Vol. 286, pages 487-491, October 1999)
- Poort et al (Blood, Vol. 88, No. 10, page 3698-3703, 1996)
- Hoon et al. (US Pat. 6,057,105, May 2, 2000)
- Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999).
- Lapointe et al. (US 6,678,669, January 2004)
- Lyamichev et al. (Nature Biotechnology, Vol. 17, pages 292-296, March 1999)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 106-124, 127-133, 135-150, 161-186, 189, 191 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol. 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol. 39, page 139-141, 1995) and La

Du (Cellular and Molecular Neurobiology, Vol. 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol. 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999).

Miller teaches screening a patient preoperatively to determine a risk for complications during a surgical procedure. Miller teaches that patients meet with the surgeon to prepare for surgery. Miller teaches that the surgeon often informs the patient of the anesthetic preoperative requirements and presents the patient with a letter. A sample letter is provided which illustrates the date of the surgery with the time, and instructions that "it is also important that your blood tests, urinalysis, and any other tests ordered by your doctor be completed two days before you are scheduled for surgery so that they can be reviewed by your anesthesiologist prior to surgery". Miller therefore teaches the importance of a blood test prior to surgery to identify any abnormalities.

Miller does not specifically teach analyzing the blood taken from the patient within two days prior to surgery for "two or more known genetic variations associated with two or more conditions".

However, Quane et al (herein referred to as Quane) teaches the detection of novel common mutations in ryanodine receptor gene (RYR1) in malignant hyperthermia (MH). Malignant hyperthermia (MH) is triggered in susceptible people by all commonly used inhalation anesthetics. Quane has identified Gly341Arg mutation which accounts

for approximately 10% of Caucasian MHS cases (abstract). Quane specifically teaches that once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided (page 471, col. 2). Quane also teaches that Arg615Cys is a substitution found in 3-5% of human MH families investigated (page 472, col. 1); Arg163Cys is a substitution found in 2-3% of MHS cases. Furthermore, three other rare mutations have been reported in the RYR1 gene which are in three isolated MHS and/or CCD cases. Quane teaches that patients which have not been indicated as MH normal should always be considered MHS clinically to avoid any possibility of the individual reacting to a triggering agent during anesthesia. Misdiagnosis of MHS individual as MHN can be lethal if such a patient is exposed to triggering agents (page 474, col. 1). Quane teaches that the mutation reported satisfies the genetic criteria necessary for demonstration of a causal mutation and as such this mutation should be of significant value for MHS diagnosis by genetic means (page 474, col. 1). Quane analyzes genomic DNA from peripheral blood for the presence of the mutations (page 474, col. 2).

Acta Anaesthesiologica Scandinavin (referred to as AAS) teaches that certain variants have a dramatic degree of resistance to the drug, succinylcholine (SC), because they destroy it so rapidly. AAS teaches that individuals show no regular metabolic disorder unless SC or mivacurium is given such that the condition is provoked. BchE mutations are dibucaine resistant, fluoride resistant or silent. SC and mivacurium are potentially toxic in people with BchE deficiency. AAS teaches that the principles of molecular biology tests and their application to BchE variants are well

illustrated and anesthesiologists need to keep up to date about these applications. AAS also teaches that other hereditary conditions of special interest to anesthesiologists, such as malignant hyperthermia, may be diagnosed by similar methods in a few years (page 141).

La Du et al (herein referred to as La Du) teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80).

Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The structures of CYP2D gene clusters are provided. The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities.

Evans et al (herein referred to as Evans) teaches the drug-metabolizing enzyme debrisoquine hydroxylase (CYP2D6) is polymorphic. Evans teaches that “inherited differences in drug-metabolizing capacity are generally monogenic traits and their influence on the pharmacokinetics and pharmacologic effects of medications is determined by their importance for the activation or inactivation of drug substrates (page 487, col. 2). Evens also teaches “the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for

example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codeine)" (page 487, col. 3). Evans illustrates in Figure 2, drug-metabolizing enzymes known to exhibit genetic polymorphisms with incontrovertible clinical consequences. Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that "many opioid analgesics are activated by CYP2D6 rendering the 2-10% of the population who are homozygous for nonfunctional CYP2D6 mutant alleles relatively resistant to opioid analgesic effects. Thus is it not surprising that there is remarkable interindividual variability in the adequacy of pain relief when uniform doses of codeine are widely prescribed" (page 489, col. 1). Evans teaches that individualizing drug dosages can improve clinical outcome (page 491, col. 1).

Poort et al (herein referred to as Poort) teaches a 20210 AG genotype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two genetic markers which are associated with thrombosis.

Moreover, Hoon et al. (herein referred to as Hoon) teaches the benefits of using multiple markers in detection assays. Hoon teaches using multiple markers provides increased sensitivity (abstract). Hoon teaches that marker combinations may be

developed, which are particularly sensitive to the effect of therapeutic regimens on disease progress such that patients may be monitored (col. 4, lines 65-68). In a particular example, Hoon demonstrates that number of markers was studied and that using four markers was significantly better than a single marker alone (col. 21).

Additionally, Hacia teaches mutational analysis using oligonucleotide microarrays. Hacia teaches that arrays of 1,480 oligonucleotide probes were designed to detect 37 known mutations, probes were spotted on surfaces to detect mutations in HBB, and BRCA1. Hacia teaches that arrays of 135,000 probes were used to interrogate the entire 16.6kb human mitochondrial genome from ten samples (page 44, col. 1). Chips have also been used for the simultaneous genotyping of 500 markers (page 45, col. 1). Hacia teaches that chips allow for unprecedented throughput in mutational analysis with a high degree of accuracy (page 46, col. 2). Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sampled patients prior to subjecting the patient to anesthetics, as taught by Miller, to determine whether they were at risk of MH, a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Quane, Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, Evans or Poort . Miller teaches that it is routine to sample patients blood to analyze the blood for

abnormalities including hematocrit levels. Miller teaches that "the laboratory evaluation should be available for review by the anesthesiologist prior to or at the time he first sees the patients preoperatively so that any questions regarding the patient's status should be resolved then and if not resolved the surgery should be delayed" (page 1325). Quane provides three examples of common mutations within the RYR1 gene which are associated with MH and which trigger MH syndrome during anesthesia, and potentially death. Quane specifically states that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" (page 471, col. 2). AAS teaches that SC and mivacurium are potentially toxic in people with BchE deficiency. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine and the variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches that codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. Evens also teaches "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codeine)" (page 487, col. 3). Additionally, Port teaches that factor V Leiden is the most common hereditary risk factor for thrombosis and two genetic markers which are associated with thrombosis.

Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within the RYR1, CYP2D6, Prothrombin, BCHE genes for the expected benefit of determining whether the patient possessed any mutations which were linked to the known condition of MH to avoid any fatal reaction to the anesthesia, for example. The ordinary artisan would have recognized that blood samples are routinely taken within two days prior to surgery and therefore to minimize inconvenience to the patient, the blood sample taken would also be an ideal sample for testing the patient for genetic abnormalities within RYR1. The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics.

The ordinary artisan would have then taken the results from the genetic tests and selected a perioperative course of action that was consistent with the results obtained from the genetic marker information. Moreover, once the selection was completed, the medical professionals would have performed the surgical procedure according to these directions to ensure the safety of the patient.

Moreover, given the teachings of Hoon and Hacia that sampling multiple markers provides increase sensitivity, the ordinary artisan would also be motivated to have sampled additional markers which are associated with complications in surgery. Therefore, the skilled artisan would have additionally analyzed a patient for a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, as taught by Acta

Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans or Poort. Given the state of the art with relation to known markers and detecting the markers as indicative of certain disease which either trigger episodes when exposed to anesthetics, or are poor metabolizers or potentially cause thrombosis are well known. The ordinary artisan would have been motivated to have screened individuals within two days prior to surgery to determine the genetic composition of the individuals to provide individualized diagnosis. Thus, the ordinary artisan would have been motivated to test patients within two days prior to surgery for mutations within any of the known genes for known mutations which are associated with known conditions for the expected benefit of determining whether the patient possessed any mutations which were linked to the known conditions such that the clinician may avoid any adverse reactions to the surgical procedure. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the vast number of teachings, as exemplified by the extremely voluminous Information Disclosure Statement filed, to screen individuals prior to surgery for several genetic markers which are indicative of any number of conditions which are caused by anesthesia or are a result of anesthesia. Hacia teaches that large numbers of probes are placed on arrays for the express benefit of high-throughput mutational analysis with a high degree of accuracy (page 46, col. 2). The ordinary artisan would have recognized that the art provides a large number of single nucleotide polymorphisms or other variations which are indicative of conditions. The benefit of screening individuals for several of these prevalent mutations which are related to surgery would have allowed the anesthesiologist to determine whether

plausible substitutes may be provided to patients which would not cause these conditions to arise. Specifically, detection of RYR1 polymorphisms which are associated with MH would indicate to the anesthesiologist that drugs which trigger the episodes should be avoided. Moreover, codeine should be administered with care to individuals having certain CYP2D6 mutations. Combining more than one screening method to determine the genomic profile of a patient would have provided the anesthesiologist with a more complete picture of the patients' genetic make-up. As suggested in many of the articles, individual treatment and screening is ideal for analysis of the genetic make-up of patients.

With respect to the claims drawn to invasive and non-invasive surgery, anesthesia and codeine, for example are administered routinely in each of these situations.

With respect to the claims drawn to specific numbers of markers, for example 5 and 10 or more mutations, the skilled artisan would be motivated to screen makers which were well known at the time of the art simultaneously or in tandem for the benefits of providing the most complete amount of information possible. Hacia specifically teaches that arrays to detect mutations of approximately 500 were known in the art at the time the invention was made.

With respect to Claim 149, the newly added limitations are all directed to obtaining consent, and distributing the results according to patient's preference. Miller specifically obtains consent based upon the consent form and signature on page 1325 of Miller. Furthermore, the results of the analysis that the patient is receiving would be

distributed to those individuals who could make an informed decision to the course of action. These individuals would be according the patience preference.

With respect to Claim 187-188, Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded.

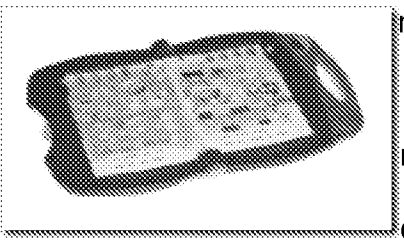
2. Claims 151-160, 187-188, 190 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol. 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol. 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol. 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol. 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) as applied to Claims 106-124, 127-133, 135-150, 161-186, 189, 191 above and further in view of Lapointe et al. (US 6,678,669, January 2004).

Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia do not specifically teach processing and selecting medical tests using computer programs to predict information.

However, Lapointe teaches obtaining patient data or information, typically patient history or clinical data, and analyzing by the decision-support systems to identify

important or relevant variables and decision-support systems are trained on the patient data. Lapointe specifically illustrates in Figure 2, the interaction of the biochemical and the computer network to generate predictive information. As seen in Figure 13 and 16, the input of data spots out test report forms that are understandable and translate into treatment options. The decision-support systems are employed to evaluate specific observation values and test results, to guide the development of biochemical or other diagnostic tests, too assess a course of treatment, to identify new diagnostic tests and disease markers, to identify useful therapies, and to provide the decision-support functionality for the test. Lapointe teaches that the final set of networks is trained to perform the diagnosis. Lapointe teaches that the biochemical tests can include any test from which useful diagnostic information may be obtained.

Therefore, it would have been prima facie obvious at the time the invention was made to have designed a neural network as taught by Lapointe for the perioperative screening method of Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia. Lapointe specifically teaches that biochemical data is inputed from patient data and analyzed to produce guides to medical personnel to assess course of treatments. The ordinary artisan would have been motivated to have automated the analysis to enable non-biochemically inclined individuals to understand the output of genomic studies in an understandable and useable manner. Lapointe specifically illustrates throughout the document the outputs provided from the software contains the meanings of the results in plain language. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known



methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time the invention. Specifically, the ordinary artisan in the biochemical fields would have found it obvious to update the biochemical assays which required analysis and reading by a human with modern networks and decision trees on a computer, as taught by Lapointe, in order to gain the commonly understood benefits of such adaptation such as increased reliability, understandable readout, and simplified operation. See Leepfrog v. Fisher-Price (Fed. Cir. 2007).

3. Claim 185 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol. 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol. 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol. 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol. 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics Supplement. Vol. 21, pages 42-47, January 1999) as applied to Claims 106-124, 127-133, 135-150, 161-186, 189, 191 above and further in view of Lyamichev et al. (Nature Biotechnology, Vol. 17, pages 2925-296, March 1999).

Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia do not specifically teach analyzing DNA using structure-specific cleavage of oligonucleotide probes assay.

However, Lyamichev teaches polymorphism detection and identification using quantitative detection of genomic DNA by invasive cleavage of oligonucleotide probes. Lyamichev specifically teaches that the invader assays are sensitive and specific to allow discrimination of single-base differences and can differentiate homozygotes from heterozygotes in single-copy genes in genomic DNA. Lyamichev teaches that a major advantage of the invader assay is the requirement for coordinated action of the invasive and signal probes. The probes together confer a high degree of specificity and simplicity.

Therefore, it would have been prima facie obvious at the time the invention was made to have modified the detection methods of Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia to encompass invader directed analysis as taught by Lyamichev. Lyamichev specifically teaches the invader assays are simple, specific and highly sensitive to avoid false positive results.

4. Claims 125 and 134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) in view of Quane et al (Human Molecular Genetics, Vol. 3, No. 3, page 471-476, 1994) or Acta Anaesthesiologica Scandinavica (Vol. 39, page 139-141, 1995) and La Du (Cellular and Molecular Neurobiology, Vol. 11, No. 1, page 79-89, 1991) or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) and Evans et al (Science, Vol. 286, pages 487-491, October 1999) or Poort et al (Blood, Vol. 88, No. 10, page 3698-3703, 1996) and further in view of Hoon et al. (US Pat. 6,057,105, May 2, 2000) and Hacia (Nature Genetics

Supplement. Vol. 21, pages 42-47, January 1999) as applied to 106-124, 127-133, 135-150, 161-186, 189, 191 above and further in view of the specification (Tables 1-4).

Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia do not specifically teach profiling for each of BchE, CYP2D6, MTHFR, MTR, CBS, F2, F5, RYR1, CACNA1S, CTP2, and TNFA.

The instant specification teaches markers in each of these genes which are associated with various operative related disorders. The specification clearly illustrates genes and mutations which are associated with the particular mutations (see page 48-49 and the cited references). The response filed March 26, 2001 specifically illustrates that the invention does not claim discovery of newly identified DNA sequences (page 7).

Therefore, it would have been obvious in view of the teachings of Miller, Quane, AAS, LaDu, Pharmoacogenetics, Poort, Hoon and Hacia to include any number of genes on the array of Hacia for the high throughput analysis of operatives complications that were known at the time of the invention. The prosecution history of this application indicates that the invention does not claim discovery of newly identified sequences, thus, it would have been obvious to include the analysis of any of the known mutations in the art.

(10) Response to Argument

Would it have been obvious to the ordinary artisan to screen for genetic mutations that were known in the prior art to trigger negative syndromes/effects in response to anesthetics prior to providing anesthetics before surgery, select an appropriate course of action and then perform the surgical procedure?

The Appellant traverses the rejection. The response filed June 14, 2007, March 11, 2008 and the brief filed August 27, 2009 asserts that the cited art fails to establish prima facie obviousness.

As a preliminary matter, the MPEP specifically states in 706.07(h), "In addition to the res judicata effect of a Board of Patent Appeals and Interferences decision in an application (see MPEP § 706.03(w)), a Board decision in an application is the "law of the case," and is thus controlling in that application and any subsequent, related application." The applicant had the opportunity to appeal any Board decision from which they were dissatisfied. Further, it is noted that as provided in 35 U.S.C. 141. "An applicant dissatisfied with the decision in an appeal to the Board of Patent Appeals and Interferences under section 134 of this title may appeal the decision to the United States Court of Appeals for the Federal Circuit. By filing such an appeal the applicant waives his or her right to proceed under section 145 of this title."

The claims are drawn to testing two or more nucleic acid markers in two or more genes associated with two or more conditions, selecting a course of action consistent with the information from the testing and performing a surgical procedure consistent with the information. The Appellant asserts that the Examiner has failed to establish a prima facie case of obviousness. This argument has been thoroughly reviewed, but is not found persuasive. The prior art teaches

- A method of performing perioperative screening to provide biological information about the patient within 72 hours of the surgery (Miller)
- Once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided (Quane). Mutations are taught which are associated with MH.
- Numerous mutations in numerous genes which are associated with toxicity, decreased or increased efficiency, ineffective response to various operative drugs (Quane, De Lu, AAS, Poort, Evans, for example)
- Methods using multiple markers provide increased sensitivity over methods employing single markers (see Hoon)
- Arrays for high-throughput and highly accurate mutational analysis which may be used for as many as 500 mutations (Hacia).

The examiner has set forth a prima facie case which combines all of the teachings and motivations specifically enumerated in the art to obtain the claimed invention as a whole and relies upon common sense (see rejection above). The holding

of *KSR* specifically rejects the rigid TSM test and finds that the references need not provide a specific motivation in the references. The cited passage from *KSR* illustrates an analysis must be made specific, not that the TSM is explicit. The analysis of *KSR* allows for a person with ordinary skill to have good reason to pursue known options within his or her technical grasp. Moreover, *KSR* discusses the use of ordinary skill and common sense. Thus, the rigid test of TSM is no longer required to be explicitly found within the references. The express teaching in Quane that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided" provides explicit motivation for testing individuals prior to anesthetics to avoid triggering MH. The ordinary artisan would have been motivated to have avoided triggering MH by performing the genetic testing taught by Quane. Quane teaches "avoiding" particular anesthetics upon diagnosis of susceptibility. It logically follows that there are two times to test for polymorphisms, before a surgery or after a surgery. The art teaches that many mutations are associated with death due to anesthesia or additional conditions which inflict pain or suffering on the individual. While one may want to investigate after death or after a survival of a clinical episode of MH, it is more likely that the ordinary artisan would want to prevent death or pain and suffering inflicted due to the response to anesthesia. Quane teaches that once the individual is diagnosed as being susceptible to MH, the anesthetics which trigger the syndrome can be avoid. Quane thus contemplates and suggests avoiding death and pain and suffering. Since Quane also teaches that "the subclinical nature of MH makes its early diagnosis difficult" the ordinary artisan would turn to genetic detection of polymorphisms

for diagnosis of MH. Testing additional known mutations which have been associated with conditions that are related to surgery or anesthesia, for example, would have been desirable to avoid the respective negative effects they have.

In light of the teachings in the art, the ordinary artisan would have been motivated to have not administered SC and mivacurium to people with BchE deficiency because the art teaches they are potentially toxic. The ordinary artisan would have been motivated to have screened for BCHE deficiency to ensure that they were not providing a potentially toxic drug to their patient. Third, the ordinary artisan would have been motivated to screen for butyrylcholinesterase variants ensure that their patients received the necessary dose of relaxant succinylcholine to achieve the desired state of paralysis. Fourth, since individuals with poor metabolism experience therapeutic failure to codeine, the discovery and identification of polymorphisms in desbrisoquine hydroxylase (Cytochrome P4502D6) saved some lives and may prevent future fatalities or morbidities. The ordinary artisan would be motivated to prevent fatalities and morbidities by testing for polymorphisms in genes. Fifth, given the teachings in the art that "the effects can be profound toxicity for medications that have a narrow therapeutic index and are inactivated by a polymorphic enzyme (for example, mercaptopurine, azathioprine, thioguanine, and fluorouracil) or reduced efficacy of medications that require activation by an enzyme exhibiting genetic polymorphism (such as codeine)" (page 487, col. 3). Further, severe and potentially fatal hematopoietic toxicity that occurs when thiopurine methyltransferase-deficient patients are treated with standard doses of azathioprine or mercaptopurine. Evans teaches that individualizing drug

dosages can improve clinical outcome (page 491, col. 1). The ordinary artisan would be motivated to avoid profound toxicity, reduced efficacy or fatality by testing for polymorphisms. Finally, genetic markers for venous thrombosis in patients have been identified. The ordinary artisan would have been motivated to screen for genetic markers know to be associated with venous thromboembolism to enable early detection and avoid the serious effects.

Overall, the prior art provides a large body of art teaching mutations which are associated with diseases or conditions. The ordinary artisan would have been motivated to have assayed for genetic markers prior to surgery to enable the detection of markers which are negatively associated with surgical conditions so that the conditions may be avoided. Miller teaches that blood samples are taken within 72 hours prior to surgery. The ordinary artisan would have been motivated to have used the blood sample drawn at this point to analyze additional genetic markers such as those taught in the art. Since a blood sample was being taken 72 hours prior to surgery, the ordinary artisan would have been motivated to have avoided an additional blood draw and would have been motivated to have used the blood sample take during this period of time. Minimizing the unneeded discomfort of a patient is of considerable concern by professionals in the medical field.

VII.A. Ground of Rejection 1

Appellant reviews the case law of *Graham v. John Deere Co., KSR Int'l Co. v. Teleflex* and *Takeda Chem. Indus., Ltd. v. Alphapharma Pty., Ltd*. (see page 19 of brief

filed August 27, 2009). Appellant then finds that the Office erred in finding all elements of an obviousness rejection were met.

VII.A.1. Ordinary level of skill in the art.

Appellant asserts that the Office never provided any evidence of any kind to back up the findings as to what an ordinary artisan would have recognized or been motivated to do. The Appellant states the Office recognizes an anesthesiologist as one of ordinary skill in the art. This argument is reviewed. While the Examiner agrees that an anesthesiologist may be one of ordinary skill in the art, the Examiner also recognizes Quane as one of skill in the art. Quane clearly recognized the benefit of testing an individual prior to surgery to avoid triggering MH. An ordinary artisan would encompass a molecular biologist who performs diagnostic assays as well as an anesthesiologist.

Appellant, relying on an anesthesiologist as the only ordinary artisan skilled in the art,states that the Declaration of Kirk Hogan, MD. overcomes the examiners findings of obviousness. The Federal Circuit, in *Leapfrog v. Fisher Price* held that "[t]he district court explicitly stated in its opinion that *Leapfrog* had provided substantial evidence of commercial success, praise, and long-felt need, but that, given the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion that claim 25 would have been obvious." *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1158-59 (Fed. Cir. 2007). Here, similar to in *Leapfrog*, the secondary considerations presented by Appellant were unable to overcome the strength of the prima facie obviousness case.

First, Appellant relies upon a conclusion by Dr. Hogan, that "[t]he ordinary artisan did not clearly recognize the benefit of testing an individual prior to surgery and subject to anesthesia for known genetic markers associated with conditions triggered by anesthesia or surgery at the time the invention was made." Second Declaration of Kirk Hogan, M.D., page 2, item 11. The objective evidence to support this conclusion is the Task Force Practice Advisory of Preannesthesia Evaluation. When reviewing the underlying evidence found in the Task Force document, the grant was rejected by a panel of experts because "the state of the art teaches that such methods should not be carried out". Based upon the committees excerpt, the committed states that "the committee's concern and reason for not funding the study rested on a few factors. It is a basic science study without clear clinical value. In the values equation the committee members considered the study might improve the quality but the cost could be very high". While Appellants are arguing that the art is not routinely doing perioperative analysis, this is not the standard for obviousness. It is noted that the claim does not require "routine perioperative analysis." There is no requirement that the method be performed routinely. The claim is drawn to a method of perioperatively screening a patient. There are many factors, such as family history, abnormal test results which may motivate a patient or physician to perform a screening method on a particular patient. As provided by the statute of 103,

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

The statute does not provide that cost is a factor in considering non-obviousness. The committee does not appear to be establishing that given the art at the time of filing, that the invention was non-obvious, but the committee rather appears to be indicating that they do not think that the idea is a cost effective study. The committee has stated that "as anesthesia practice has moved toward determining the ratio or quality to cost, this study seems to be going in the opposite direction". This statement is directed to the economical benefits of sampling individuals prior to surgery not the obviousness of studying individuals prior to surgery. The Board previously addressed the economical argument, in their decision of July 25, 2006, and relying upon *In re Farrenkopf*, found a method can be properly considered obvious even if it would have been more expensive than alternative methods (pages 13-14 of the Board Decision in 09/613,887, July 25, 2006). Furthermore, the factors considered when determining whether to fund a particular study are completely different than the factors considered in determining that an invention is legally patentable. Grants are often funded because they offer an immediate use, return on value or information that the community may build upon. These are not the criteria which must be met to obtain a patent or to show non-obviousness of the prior art references. The Appellant argues that "this objective evidence of non-obviousness, confuses the fact of non-obviousness ("it would take the issue of patient safety in a new direction"), with the reasons for non-obviousness i.e. cost, confidentiality, ethics." The examiner agrees that the reasons, i.e. cost effectiveness, etc. are immaterial to the finding of non-obviousness, therefore, the reasons given in the grant study are not material to the finding of non-obviousness. The

Appellant argues that the Examiner is distracted by cost and economic benefit analysis (page 21 of response). This argument has been thoroughly reviewed, but is not found persuasive because the examiner provide analysis as to why cost is not a consideration in determining obviousness.

The second declaration of Kirk Hogan, filed July 8, 2002, has been thoroughly considered, but found not persuasive. The declaration asserts that the state of the art has not tested subjects for genetic markers during the perioperative period. The declaration reviews a Practice Advisory for Preanesthesia Evaluation: A report by the American Society of Anesthesiologist Task Force on Preanesthesia Evaluation. The declaration asserts that no perioperative genetic testing of any kind is advocated, discussed or mentioned. This silence with respect to genetic testing does not mean that the testing would be unobvious. While the article may not specifically consider genotypes for preanesthesia evaluation does not provide evidence that the combination of the cited references do not provide the legal standard for obviousness. The teachings of the article are not directed to the non-obviousness of the invention. The examiner has set forth objective evidence in the form of references to establish a prima facie case of obviousness. The Appellant has selected certain passages from the evaluation which do not appear to represent the full teachings of the reference. The Practice Advisory for preanesthesia evaluation states that the study is intended to assist decision-making in areas of patient care, but not intended as guideline, standards or absolute requirements. The evaluation may be “adopted, modified or rejected according to clinical needs and constraints” (abstract). Moreover, preoperative tests

may be indicated for various purposes including discovery or identification of a disease or disorder that may affect perioperative anesthetic care. It is noted that MH as taught by Quane is a disorder which will affect preoperative anesthetic care. Therefore, the reference does not appear to support the assertion that preoperative care precludes the testing of genetic markers. "The Task Force agrees that preoperative tests may be ordered, required, or performed on a selective basis for purposes of guiding or optimizing perioperative management. The indications for such testing should be documented and based on information obtained from medical records, patient interview, physical examination and type and invasiveness of the planned procedure" (page 490, col. 1-2). Moreover, the Task force "believes that there is insufficient evidence to identify explicit decision parameters or rules for ordering preoperative tests on the basis of specific clinical characteristics" (page 490, col. 1-2). Note 4, states that "selective preoperative tests (i.e., tests ordered after consideration of specific information obtained from sources such as medical records, patient interview, physical examination and the type of invasiveness of the planned procedure and anesthesia) may assist the anesthesiologist in making decisions about the process of preoperative assessment and management" (page 493, col. 1). Therefore, based upon the teachings of the reference as a whole, the reference does not state that preoperative tests should not be done.

VII.A.2 Motivation to Combine Miller in view of Quane or Acta or La Du or Pharmacogenetics or Evans or Poort and further in view of Hoon and Hacia.

Appellant submits that the Office has used improper hindsight reconstruction to formulate the rejection. The Appellant contends that there was no explicit or implicit teaching or suggestion or motivation to combine the elements present in the art. Appellant concludes that the Office's rejection has not been specific or provided evidence that the claims were within the technical grasp of one of ordinary skill in the art at the time the invention was made.

Appellant then turns to Dr. Coursin's declaration to explain there was no suggestion or teaching in the prior art or elsewhere for the perioperative genomic profiles of the presently claimed invention. It is noted that Dr. Coursin uses the word "novel" which is associated with novelty and not obviousness. Dr. Coursin states he is unaware of any one previously proposing or disclosing perioperative genomic profiles. This passage was thoroughly considered but not found sufficient to overcome the prima facie case of obviousness. Extensive motivation to combine the cited references is given in the rejection.

Appellant uses the words "failure of an entire field to solve the primary problem" which may be an attempt to overcome the rejection using the long-felt need or failure of others secondary consideration, however, the elements for such a secondary consideration has not been met. Appellants have not shown the elements necessary for a failure of others declaration. The declaration under 37 CFR 1.132 filed on June 14, 2007 is insufficient to overcome the rejection as set forth in the last Office action because: it states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art

were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04. Here, the declaration of Dr. Coursin fails to provide any evidence in the opinion declaration that the ordinary skilled artisans were working on the problem and for how long. Appellant argues that artisans of ordinary skill have been highly motivated to detect multiple risks for complications before, during and after a surgical procedure associated with genetic variations for 26 years "and well before." A reading of the passage in Dr. Coursin's declaration appears to state something different. The declaration appears to state that Dr. Coursin has been practicing Anesthesiology for 26 years. This is much different than he has been trying to solve the problem of detecting multiple risks for complications with genetic variations, as characterized by the brief (page 27 of the brief filed August 27, 2009). The passage cited by the brief does not even use the words genetic variations.

Moreover, the declaration fails to provide any evidence that those working in the art on the problem knew of the Quane, Miller, Acta Anaesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans et al, Poort et al , Hoon et al. or Hacia references and were still unable to solve the problem. Thus, the declaration is insufficient to overcome the 103 rejection of record. In the response filed March 11, 2007, the response appears to confirm that the skilled artisans would not have looked and did not look the Examiner's art (see page 42 of the response). Rather than meeting the evidentiary

standard required for long-felt need, Applicant misses the point and heads in a different direction.

Appellant argues that the rejection fails to place in the hands and minds of the appropriate skilled artisan the prior art of record and the mental and experimental process for modifying the art to arrive at the inventions. *In re Winslow* discuses that we should "first picture the inventor as working in his shop with the prior art references- which he is presumed to know- hanging on the walls around him." *In re Winslow*, 365 F.2d 1017 (CCPA 1966). The court in *Winslow* continues "[s]ection 103 requires us to presume full knowledge by the inventor of the prior art in the field of his endeavor." Here, the ordinary artisan working in "his shop" would be apprised of each of the references. Moreover, extensive guidance is given in the rejection as to how the references would be combined to arrive at the claimed invention.

Finally, Appellant argues Dr. Coursin explains that he himself has since used embodiments of the invention and achieved excellent, and unexpected results. As provided in MPEP 716.02(a) evidence must show unexpected results. The opinion declaration submitted by Dr. Coursin does not appear to show any unexpected results. The declaration provided by Dr. Coursin, states that many genetic markers were found to exist in patients and that there was significant genetic heterogeneity not accounted for in family history check-boxes. The discovery that individuals contain heterogeneity is not unexpected. The art of record clearly illustrates the frequency of various alleles within the population. It is not unexpected that screening for genetic mutations known to be associated with deleterious outcomes and death, are present in humans. In fact it

is completely expected given all of the teachings of the art. Moreover, it is completely not unexpected that detecting these genetic mutations can avoid deleterious outcomes and save lives. This is the basis of the entire 103 rejection.

VII.A.3. Missing Elements

Appellant submits the combination fails to disclose multiple elements of the invention (page 31 of Brief filed August 27, 2009). Appellant asserts that none of the additional 8 references in combination teach "two or more known genetic markers associated with two or more conditions." This argument is wrong. MH, a dramatic degree of resistance to the drug, succinylcholine (SC), resistant to succinylcholine, desbrisoquine hydroxylase, or venous thromboembolism, are taught by Quane, Acta Anaesthesiologica Scandinavica, La Du , Pharmacogenetics, Evans or Poort . Six references are provided to teach more than 5 different conditions associated with at least 5 different genetic markers.

II.A.3.a. The response asserts Claim 106 requires selecting a perioperative course of action based upon information from the genomic profile. The examiner fully agrees with this assertion. However, given the cited combination of references, once the ordinary artisan realized that a patient was predisposed to have an adverse reaction to anesthesia or other condition, the ordinary artisan would have selected a course of action consistent with this discovery and acted appropriately. Doctors are subject to liability. In the event that the skilled doctor did not heed the warnings of a genetic test

performed, liability would attach. Thus, the ordinary artisan would have been motivated to have taken what was determined and discovered from the genetic profile and used the information in a prudent manner to avoid any complications that may exist given the information generated from the genetic analysis.

Preliminarily, the Board has previously decided this issue (see Board decision for 09/613,887, mailed July 25, 2006, page 16, discussion of Claim 102). As previously argued and affirmed by the Board, it would have been obvious once the genomic profile was determined, that a perioperative course of action based on the information from the profile would be followed. It is clear that previous Claim 86 from appeal already positively recited this additional method step and was affirmed by the Board.

The Brief filed August 27, 2009 and response filed March 11, 2008 states that the examiner's observations are conclusory and unsupported by any evidence; uses speculation as to what the ordinary artisan would have been motivated to do and the analysis regarding professional liability does not remedy the defects (Brief page 32). This argument has been reviewed but is not persuasive. KSR recently evaluated the standard required for obviousness. When an examiner's findings of fact are based on common sense, the examiner must provide an explanation as to why the difference would have been obvious. Here, the examiner has provided an analysis for why a medical professional would have selected a perioperative course of action based upon genetic information obtained from an analysis and known to be associated with a condition. KSR forecloses the argument that a specific teaching suggestion or motivation is not required to support a finding of obviousness. KSR finds that “rigid

preventative rules that deny recourse to common sense are neither necessary under, nor consistent with, this Court's case law." Here, it would appear to be common sense to follow the results of the genomic profile to select a perioperative course of action. It would lack common sense to obtain a result that a patient with a particular combination of genetic markers would be adversely affected by anesthesia X, and possibly die, and then administer anesthesia X.

Appellant asserts that the references fail to provide any guidance to the anesthesiologist, nurse or surgeon to use the information (see page 33 of the Brief filed August 27, 2009). This argument has been reviewed but is not persuasive. The information obtained from a genomic profile would be information that the surgeon, anesthesiologist and nurses would use. For example, Quane teaches variants in the RYR1 gene which are associated with poor response to anesthesia. The rejection above further outlines additional references which teach association between genetic markers and response to anesthesia or drugs used in surgery. This information would be information appropriate for anesthesiologists to have in order to prescribe and administer the appropriate anesthesia to a patient. Here, the examiner has provided an analysis for why a medical professional such as a nurse, surgeon or anesthesiologist would have selected a perioperative course of action based upon genetic information obtained from an analysis and known to be associated with a condition. KSR forecloses the argument that a specific teaching suggestion or motivation is not required to support a finding of obviousness. KSR finds that “rigid preventative rules that deny recourse to common sense are neither necessary under, nor consistent with, this Court's case law".

Here, it would appear to be common sense for a nurse or surgeon or anesthesiologist to use this information, as they are the medical professionals involved.

II.A.3.b. Appellant argues that the combination of references is missing the limitation that a perioperative course of action is for the first surgical procedure for the subject (claim 107). This argument has been reviewed but is not persuasive. As argued above, once the ordinary artisan knows a patient has a marker that will result in adverse effects, it would be common sense to administer a treatment that would not result in the adverse effect. Moreover, the ordinary artisan would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent any complications. The response asserts that Quane reference merely suggests testing after a patient has had a prior complication during a surgical procedure. This argument has been reviewed but is deemed not persuasive because it would be common sense to test for a mutation known to be negatively associated with surgical procedures prior to surgery to prevent complications, as previously stated.

II.A.3.c Appellant argues that the combination of references is missing the limitation that the course of action based upon information from a perioperative genomic profile comprise administration of anesthesia during a medical procedure (Claim 117, 168). This argument has been reviewed but is not persuasive. As argued above, once the ordinary artisan knows a patient has a marker that will result in adverse effects, it would be common sense to administer a treatment that would not result in the adverse

effect. In particular, the Quane references teaches that "once an individual is diagnosed as being susceptible to MH, the anesthetics which trigger this syndrome can be avoided." This passage illustrates that not ALL anesthesia is avoided, but those that trigger this syndrome are avoided. Thus, the course of action would contain anesthesia, but be modified to include an anesthetic which does not trigger MH.

The response attacks Quane individually, but fails to consider the combination of references for teaching perioperative genomic profile for administration of anesthesia during a medical procedure. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

II.A.3.d Appellant argues that the combination of references is missing the limitation that the genomic profile comprises information comprising presymptomatic risk (Claim 120). This argument has been reviewed but is not persuasive. The ordinary artisan given common sense would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent any complications before signs are shown. The ordinary artisan would be motivated to test for MH and other conditions prior to triggering a response that would cause death. Appellant argues the missing elements are not met with evidence. The examiner instead relies upon common sense. It is also noted that the method necessarily provides a presymptomatic diagnosis of risk

for adverse effects- the diagnosis of risk for adverse effects is made prior to any showing of symptoms of adverse effects.

II.A.3.e. Appellant argues that the combination of references is missing the limitation that the genomic profile comprises information pertaining to differential diagnosis of co-existing diseases (limitations of Claim 121). This argument has been reviewed but is not persuasive. The combination of references shows there are a variety of co-existing conditions that may cause adverse effects. The genomic profile suggested by the combination of references is necessarily a property. The analysis of the MH gene would allow for differential diagnosis between MH and other anesthesia triggering conditions. Once the differential diagnosis is performed the appropriate response by the medical professional can be performed.

II.A.3.f. Appellant asserts Claim 127 requires selecting a surgical procedure treatment course of action based upon information from the genomic profile. The examiner fully agrees with this assertion. However, given the cited combination of references and common sense, once the ordinary artisan realized that a patient was predisposed to have an adverse reaction to anesthesia or other condition, the ordinary artisan would have selected a course of action consistent with this discovery and acted appropriately. Doctors are subject to liability. In the event that the skilled doctor did not heed the warnings of a genetic test performed, liability would attach. Thus, the ordinary artisan would have been motivated to have taken what was determined and discovered from

the genetic profile and used the information in a prudent manner to avoid any complications that may exist given the information generated from the genetic analysis. Appellant argues the missing elements are not met with evidence. The examiner instead relies upon common sense.

II.A.3.g. Appellant asserts that the combination of elements fails to teach a non-invasive surgical procedure (Claim 139, 179). This argument has been reviewed but deemed not persuasive. The ordinary artisan with common sense would be motivated to screen patients for any and all surgeries to ensure precautions are taken to prevent any complications before signs are shown. The ordinary artisan would be motivated to test for MH prior to triggering a response that would cause death. Appellant argues the missing elements are not met with evidence. The examiner instead relies upon common sense.

II.A.3.h. Appellant asserts that the combination of elements fails to teach selection of monitoring procedures based upon the profile (Claim 148, 175). This argument has been reviewed but deemed not persuasive. The ordinary artisan would have been motivated to have monitored procedures. Poort specifically teaches an 20210 AG genotype of the prothrombin gene which is a candidate for venous thrombosis in patients. It is well known in the art that venous thromboembolism can occur without apparent cause, after surgical procedures or trauma. Poort also teaches that factor V Leiden is the most common hereditary risk factor for thrombosis. Poort teaches two

genetic markers which are associated with thrombosis. Thus, in the event that the patient's profile indicated the presence of markers known to be associated with venous thrombosis, the nurses and doctors would have monitored the patient more closely for signs of venous thrombosis. Appellant argues the missing elements are not met with evidence. The examiner instead relies upon common sense to take what is taught by the art and apply it to its logical conclusion.

II.A.3.i. Appellant asserts that the combination of references is missing the element of obtaining consent from a perioperative subject to assay a sample for genetic variation (Claim 149). Despite Miller teaching obtaining consent for perioperative tests and analysis, the response asserts this is not consent for a genetic variation test. This argument has been reviewed but is not persuasive. The ordinary artisan would have been motivated to have obtained consent for ANY procedure in the medical field, as is routine and customary in the field, to avoid any malpractice allegations. It is routine in the art that any procedure requires authorization and consent. Individuals who are subjected to surgery sign consent forms routinely. Thus, requiring consent from a subject prior to the perioperative genomic profiling would have been obvious in light of the routine practice in the art and the specific teachings of Miller. Miller even provides a template of a consent form, page 1325. Appellant argues the missing elements are not met with evidence. The examiner disagrees, as the art, namely Miller teaches obtaining consent forms for perioperative tests and analysis.

II.A.3.j. Appellant asserts that the combination of references is missing the element of distributing the results of a patients profile to include destroying the results or saving the results (Claim 149, 189). This argument has been reviewed but is not persuasive. The ordinary artisan would have either destroyed the results or saved the results. It is not apparent what other choices were available to the patient. In one instance, the patient may expect to require additional surgery in the future and wish to save the information to be used at a later date. Thus, the ordinary artisan would have been motivated to have done one of these two actions. Appellant argues the missing elements are not met with evidence. The examiner instead relies upon common sense.

II.A.3.k. Appellant asserts that the combination of references is missing the element of distributing the sample to include destroying the sample or saving the sample (Claim 149 and 189). This argument has been reviewed but is not persuasive. The ordinary artisan would have either destroying the sample or saving the sample. It is not apparent what other choices were available to the patient. In one instance, the patient may expect to require additional surgery in the future and wish to save the sample to be analyzed at a later date. Thus, the ordinary artisan would have been motivated to have done one of these two actions. Appellant argues the missing elements are not met with evidence. The examiner instead relies upon common sense.

II.A.3.l. Appellant asserts that the combination of references is missing the element of a computer program comprising instructions which direct a processor to analyze results of

a perioperative genomic profile (Claim 150). This argument has been reviewed but is not persuasive. Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded. Appellant argues that Hacia fails to remedy the rejection because Hacia fails to discuss perioperative genomic profiles. This limitation is met with other references in the combination such as Miller, Quane, Acta, La Du, Evans, and Poort.

II.A.3.m. Appellant asserts that the combination of references is missing the element of detecting MTR, MTRR and CBS. As noted above, the specification clearly illustrates genes and mutations which are associated with particular mutations. The specification, pages 48-49 clearly illustrates the genes of the claims and the cited references. Moreover, the prosecution history clearly states that the invention does not claim discovery of newly identified DNA sequences (page 7). Thus, the ordinary artisan would have profiled the genes recited in the claims to enable the analysis of the particular conditions associated with the alleles.

II.A.3.n. Appellant asserts that the combination of references is missing the element of teaching of a kit comprising a computer program (Claim 186). This argument has been reviewed but is not persuasive. The response first asserts that the Office has misread the claim. Appellant asserts the claim is directed to a kit comprising a computer

program on a computer. Upon reading the claim, Claim 186, is directed to a method of Claim 149, and thus is directed to a method that uses a computer program.

The use of computer programs to analyze data, was specifically illustrated by Hacia. Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The use of a computer program on a computer would meet the limitations of the instant claims. In Hacia, the data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded. The providing of the computer and algorithm meets the requirements of a kit. A kit, without more, is merely a composition of reagents. Since Hacia teaches the computer program on a computer, there is no missing element as suggested by the Appellant.

II.A.3.o. Appellant asserts that the combination of references is missing the element of teaching of a kit for generating a perioperative genomic profile (Claim 186). This argument has been reviewed but is not persuasive. The use of computer programs to analyze data, and generate results, i.e. genomic profile, was specifically illustrated by Hacia. Hacia teaches mutations are detected by a minisequencing assay using an algorithm. The data obtained is placed in a computer which is encrypted, but accessible to readers, i.e. decoded. The providing of the computer and algorithm meets the requirements of a kit. A kit, without more, is merely a composition of reagents. Since Hacia teaches the computer program on a computer, there is no missing element as suggested by the Appellant.

II.A.3.p. Appellant asserts that the combination of references fails to teach selecting the markers by analytical validity, clinical validity and clinical utility (Claim 189). This argument has been reviewed but is not persuasive. The ordinary artisan would have selected those markers, as discussed above, based upon these three criteria. Analyzing markers which have no utility or validity would not have been motivated by the art. Appellant argues the missing elements are not met with evidence. The markers taught by all of the references above are of clinical utility, clinical validity and analytical validity. There is no missing element from the rejection above.

II.A.3.q. Appellant asserts that the combination of references fails to teach selecting genetic markers consisting of unique genomic identifiers (Claim 191). This argument has been reviewed but is not persuasive. The claims provide a very long Markush list of which unique genomic identifiers is the last element. The combination of references undeniably comprises selecting markers of pharmacogenetic risk, genetic markers of outcomes of a surgical procedure, genetic markers to predict postoperative outcomes, as also recited in Claim 191. Thus, there is no missing element.

VII.A.4. Appellant asserts that the Office has erred in determining the scope and content of the prior art. Appellant points out three claims that do not require RYR1 or malignant hyperthermia, for example. The examiner agrees that these claims do not require these elements. However, the rejection includes numerous additional references for the genetic markers for the required genes or conditions.

With respect to codeine and BchE, the appellant correctly points out the Examiner's typographical error. Evans teaches CYP2D6 is involved in codeine metabolism.

VII.A.5 Appellant asserts that Claims 143-148 are not obvious and have not been examined. Claim 143 requires analyzing genes associated with butyrylcholinesterase deficiency and impaired debrisoquine metabolism. La Du et al teaches butyrylcholinesterase variants which have been found in individuals who have responded abnormally to the muscle relaxant succinylcholine. Variants with increased activity are resistant to succinylcholine and may require two or three doses to achieve the desired state of paralysis (page 80). Pharmacogenetics teaches polymorphisms of desbrisoquine hydroxylase (Cytochrome P4502D6). The poor metabolizers are depicted. Pharmacogenetics teaches that for drugs such as codeine and encainide it is the PM subjects who may experience therapeutic failure (page 317, col. 1). Codeine is ineffective analgesic in the 5-10% of the population who have a PM phenotype. The discovery and identification of each of these conditions has saved some lives and may prevent future fatalities or morbidities. The art teaches markers associated with each of these conditions. Quane provides an additional explicit motivation to avoid markers known to have negative effects with anesthesia.

With respect to Claim 144, the claims require any markers associated with adverse responses to anesthesia treatment. Each of the markers cited above would be encompassed within this very large genus of markers.

VII.B Appellant relies upon the arguments presented above for Claim 149 or 189 for the allowability of Claims 151-160, 187-188. As explained in great detail above, Claim 149 and 189 are not allowable. The response asserts that the Office's combination fails to teach or suggest privacy, privacy security or the privacy protocols of 187 and 188. At the time the invention was made, privacy issues were essential to medical records and the ordinary artisan would have been aware of the need for privacy. With respect to Claim 190, Appellant asserts that the art does not teach distributing the results of a patient's profile according to the patient's preference. Upon review of Claim 190, the claim does not require any patient preferences. Finally, Appellant argues that Lapointe does not teach or suggest characterization of DNA and there would be no expectation of success. Lapointe teaches obtaining patient data or information, typically patient history or clinical data, and analyzing by the decision-support systems to identify important or relevant variables and decision-support systems are trained on the patient data. Lapointe teaches that the final set of networks is trained to perform the diagnosis. Lapointe teaches that the biochemical tests can include any test from which useful diagnostic information may be obtained. While Lapointe does not specifically teach analysis of DNA, Lapointe uses the data obtained from the analysis, which invites the analysis was performed. The response asserts there is no expectation of success, however, fails to set forth any analysis. Lapointe teaches analysis of data. There would have been a reasonable expectation of success if the data from Quane, ACTA, La Du,

Evans or Poort, for example, were used in Lapointe, the results could be analyzed and diagnosis could be performed.

VII.C Appellant relies upon the arguments presented above for Claim 149 for the allowability of Claims 185. As explained in great detail above, Claim 149 is not allowable. The response further asserts there would be no expectation of success, but fails to set forth any analysis. Lyamichev teaches an invader directed analysis which was routine in the art at the time the invention was made and applied to numerous genes and mutations for analysis.

VII.D. Appellant relies upon the arguments presented above for Claims 106 and 127 for the allowability of Claims 125 and 134. As explained in great detail above, Claims 106 and 127 are not allowable. The response asserts that the combination of references fails to teach or suggest the closed panel of alleles. This argument appears to be first presented in this appeal brief. It is noted that Claim 125 and 134 require a combination of alleles which are all known in the art. The selection of this group of alleles, known in the art, would have been obvious because each of these genes is associated with risks involved with surgery or post surgical conditions.

(11) Related Proceeding(s) Appendix

Copies of the court or Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Jeanine Goldberg/

Primary Patent Examiner

Conferees:

/David Nguyen/

Supervisory Patent Examiner

/Juliet Switzer/

Primary Patent Examiner